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Intrauterine Exposure of Human Newborns to PCBs (Polychlorinated Biphenyls) Measures of Exposure

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by

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16. ABSTRACT

The purpose of the present paper is two-fold: (1) to summarize what is known about the pre- and postnatal effects of an especially ubiquitous chemical compound, polychlorinated biphenyls (PCBs); and (2) to examine empirically some of the linkages proposed in an analytic model of PCB exposure in human infants. The linkages of interest are those between the source of contamination and the exposure of mother and infant.

The present data are consistent with the notion that PCBs move through the environment and the human body into systems which may potentially threaten the infant both before and after birth. At this time it is not clear which of these exposures--prenatal (intrauterine) or postnatal (via breast milk)--has the greater impact on infant development. While the absolute quantity of PCB residues is substantially lower in cord serum than in breast milk, the fetal organism is particularly vulnerable during the prenatal period. One factor that has been overlooked in this debate is the size of the fetus. When PCB exposure is calculated on the basis of body weight, the infant's prenatal exposure is substantial. In addition, the values for PCBs in cord serum may underestimate actual levels of exposure for reasons discussed earlier. Moreover, different biological systems in the fetus and newborn may be affected depending on the developmental period during which exposure occurs.

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INTRAUTERINE EXPOSURE OF HUMAN NEWBORNS TO PCBs: MEASURES OF EXPOSURE

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INTRODUCTION

Behavioral assessment is becoming an important tool for evaluating the consequences of intrauterine exposure to chemical agents routinely encountered in the environment (Fein et al., 1983b; Spyker, 1975). However, studies of the effects of these agents on human infants pose several special problems for research design and for the assessment of behavioral outcomes. The purpose of the present paper is two-fold:

(1) to summarize what is known about the pre- and postnatal effects of an especially ubiquitous chemical compound, polychlorinated biphenyls (PCBs); and

(2) to examine empirically some of the linkages proposed in an analytic model of PCB exposure in human infants. The linkages of interest are those between the source of contamination and the exposure of mother and infant.

Evidence from several sources indicates that PCBs cross the placenta and are teratogenic in human infants exposed at high levels. PCBs are found in umbilical cord serum at birth when exposure results from ordinary dietary sources, and maternal serum levels are moderately related to fetal serum levels (Kodama and Ota, 1980; Masuda et al., 1978; Polishuk et al., 1977). In separate incidents in Japan and Taiwan, infants of pregnant women who consumed rice oil accidentally contaminated with sizable amounts of PCBs showed elevated PCB serum levels and a set of physical characteristics (e.g., chloracne,

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brown pigmentation of the skin, swollen eyelids) known in the literature as Yusho (rice oil) disease (Harada, 1976; Higuchi, 1976; Wong and Hwang, 1981). Infants exposed in utero were small-for-gestational age and tended to be born prematurely (Funatsu et al., 1972). Follow-up studies of exposed infants reported an average IQ of 70; sluggish, clumsy, and jerky movement; apathy and hypotonia; autonomic disturbances; and growth impairment (Harada, 1976). These disturbances in responsiveness and neuromuscular organization are consistent with reports of slowed sensory and motor nerve conductance in exposed adults (Chia et al., 1981; Harada, 1976). Although PCB blood levels diminish once exposure ceases, infants born several years after the exposure of their mothers showed elevated PCB blood levels, reduced birth weight, and brown pigmentation of the skin (Abe et al., 1975; Harada, 1976).

Placental passage and fetopathy have also been demonstrated in experimental studies with mammals such as rabbits, mice, rats, and rhesus monkeys (Allen et al., 1980; Bowman et al., 1978; Chou et al., 1979; Masuda et al., 1979; Grant et al., 1971; Tilson et al., 1979). PCBs may cross the placenta more freely as gestation progresses. In mice, higher concentrations are found in the fetus, placenta, and amniotic fluid as parturition approaches (Torok and Weber, 1981).

In rhesus monkeys, prenatally exposed infants weighed less at birth than controls and by 2 months of age developed Yusho-like symptomatology. Behavioral tests given between 6 and 24 months of age revealed hyperlocomotor activity and learning retardation (Bowman et al., 1978); but when tested at 44 months of age, these animals were hypoactive relative to controls (Bowman and Heironimus, 1981). In a follow-up study, adult female monkeys were removed from their PCB diet for a 1 yr period prior to conception (Allen et al., 1980). Although the physical condition of these animals improved and PCB levels in maternal adipose tissue declined markedly, 4 of the 15 offspring were stillborn. The birth weight of the liveborn infants was reduced relative to nonexposed infants, and four infants died after weaning at 4 months of age. In these studies, animals were fed diets containing only 2.5 or 5.0 mg/kg of PCBs, levels thought at the time to be low. In rhesus monkeys, as in humans (Harada, 1976), teratogenic effects appear in infants whose mothers had consumed PCB prior to, but not during, pregnancy.

When mice were fed relatively low levels of PCBs during pregnancy (32 mg/kg on days 10-16 post-conception), some pups subsequently developed the "spinning syndrome" (Chou et al., 1979; Tilson et al., 1979). More subtle signs of neurobehavioral dysfunctioning appeared in prenatally PCB-exposed mice which did not develop obvious clinical signs of neurotoxicity. Assessments of subtle behavioral functions indicate that exposed but apparently asymptomatic mice have learning deficits and depressed neuromuscular reflexes even though PCBs are no longer detectable in their body tissues (Tilson et al., 1979). A sluggish response to a novel situation and less pronounced habituation have been observed in asymptomatic mice exposed perinatally to PCB doses below those associated with obvious neuromotor disorders (Storm et al., 1981).

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Table 1 summarizes the major assessment categories used in teratogenic assessment (Spyker, 1975) and the results of the studies reviewed above. While to date no morphological anomalies have been found to result from fetal exposure to PCBs, such exposure has been associated with clinical symptoms, maturational and growth retardation, and a variety of subtle behavioral deficits.

TABLE 1

Assessment Categories in the Evaluation of Teratogenic Effects

Assessment Category	Illustration
Morphological characteristics	Anomalies not found in PCB studies
Physical characteristics	Chloracne; brown pigmentation of skin, lips, gums; parchment-like skin; swollen eyelids, face; premature eruption of teeth
Maturational landmarks	Preterm birth (neuromuscular and physical immaturity)
Growth	Small birth size; depressed postnatal growth
Reflexes	"Spinning syndrome" in mice
Activity levels	Hypo- and hyper-activity in an open-field; clinical assessment of apathy
Neuromuscular and sensory motor capacities	Tests of coordination (swimming in mice)
Sensory and attentional functions	Deficits in visual, auditory, olfactory, or attentional functions not found; numbness reported in humans exposed in adulthood
Learning ability	Alteration and reversal learning deficits in monkeys
Autonomic regulation	Inappropriate response to stress; deficits in temperature control; tremulousness
Sexual development	Reproductive failure; menstrual irregularities

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Consumption of PCB-contaminated fish caught in Lake Michigan constitutes a major source of human exposure to PCBs, with PCB body burden directly related to amount of fish consumed ($\underline{r}$ = 0.51; Humphrey, 1976). Although epidemiological studies of acutely exposed humans and experimental studies of chronically exposed animals indicate that PCBs are injurious, there are problems in extrapolating from studies of humans acutely exposed at high levels to those exposed chronically at low to moderate levels. Even at relatively high levels of consumption of PCB-contaminated fish, chronic exposure is considerably less than that experienced in the rice oil incidents. In contaminated fish eaters, obvious and distinctive Yusho symptoms have not been noted, and infants born to mothers who consume contaminated fish are likely to be clinically asymptomatic. Analyses of the consequences are complicated because the effects of low level chronic exposure are likely to be subtle and may occur in the absence of symptoms typically associated with acute exposure. Although subtle behavioral effects appear in animals exposed to low doses of PCBs, extrapolation from animals to humans is also risky. For example, species differ in their ability to eliminate PCBs, and as a result, the dose required to produce an effect will vary among species. Animal models are an essential aspect of teratogenic testing; however, the findings of this type of research must be corroborated in studies of humans.

The present study involves two groups of humans who are particularly at risk: the pregnant woman and her newborn offspring. The study, which utilizes a prospective longitudinal design, investigates the model shown in Figure 1. In this model, consumption of contaminated lake fish, assumed to be a major source of PCB exposure, results in elevated maternal PCB levels. Elevated maternal body burden has both direct and indirect implications for the developing fetus. Since PCBs cross the placenta, the developing fetus is exposed directly to some part of the mother's body burden. Maternal body burden may also affect maternal health and reproductive capacity, which in turn may influence fetal development. PCBs are also transferred from maternal tissue to breast milk, which provides an additional source of direct exposure for breast-fed infants. In order to evaluate the contribution of these sources of exposure, infant behavioral and medical assessments are administered at birth and again at 5, 7, and 13 months.[1] The longitudinal design is necessary because the effects of low levels of exposure may not appear at birth. Further, subtle behavioral effects may appear in the absence of gross structural anomalies or obvious functional deficits long before classical symptoms of pathology become apparent (Spyker, 1975; Weiss and Spyker, 1974).

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[1]Since the fish consumption interviews were not conducted by the same persons who subsequently collected medical and behavioral data, those engaged in assessment activities were blind with respect to the mother's pattern of fish consumption and infant's potential exposure levels.

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Several available measures of PCB contamination are examined. Each of these presents its own set of problems. Since maternal and cord blood are low in lipids, PCBs are difficult to recover. Breast milk, which contains higher lipid levels, can be assessed more reliably but is biologically more removed from the infant, obtained postpartum, and only available for a limited number of women. Maternal reports of fish consumption provide an alternative measure of exposure. They summarize the history of the respondent's exposure in contrast to biological measures, which are limited to a single point in susceptible to short-term fluctuations. However, maternal recall may be inaccurate, and attempts to adjust for the contaminant levels of the particular species of fish consumed yield at best only rough approximations of exposure. In this report, relations among these various measures of exposure are used to validate critical linkages in the model described above.

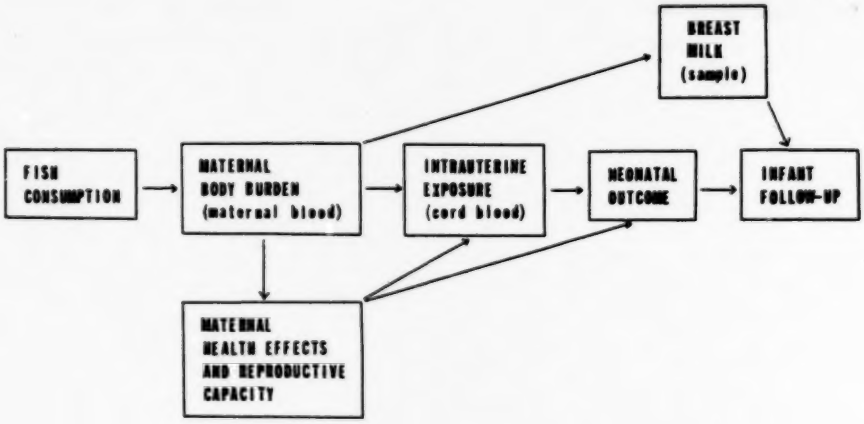

Figure 1. Model of pre- and post-natal exposure to polychlorinated biphenyls via ingestion of contaminated fish.

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METHOD

Subjects

The sample, comprised of 313 infants and their mothers, was drawn from three hospitals in Grand Rapids and one in Muskegon.[2] All mothers delivering at these hospitals were considered eligible to participate with the following exceptions: mothers had to be at least 18 years of age and have completed 10th grade in high school.

The infant sample consisted of 164 males and 149 females. The proportion of males (52%) did not differ significantly from expected (51%). All infants were white, with the exception of two black infants. Forty-three percent were firstborns. Six were the larger members of twin pairs, none of whom died during infancy. Anthropometric measures are presented in Table 2. Only one infant was below the tenth percentile on weight-for-gestational age (Lubchenco et al., 1963). One severely premature newborn (GA = 26.9 weeks, birth weight = 909 g) died. When the health status of the sample was evaluated on the Postnatal Complications Scale, the mean score was 94.1 percent optimal (Littman and Parmelee, 1978).[3] Only five infants (2.1%) had a 5-minute Apgar score below 7.

Socioeconomic status (SES) of the study sample, based on a weighted sum of father's education and occupational status (Hollingshead, n.d.),[4] was predominantly middle-middle class. Most of the fathers' occupations ranged from semi-skilled laborers to middle-level management, with only 4.5 percent classified as menial or unskilled. Almost all of the women were married and living with the father of their newborn infant.

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[2]Results of a state-wide survey of breast milk found PCB levels exceeding 2 mg/kg (fat basis) in 27 percent of the counties in the western part of the lower peninsula, in contrast to only 5 percent of the eastern counties (Wickizer et al., 1981). Grand Rapids is the largest metropolitan area located near Lake Michigan. The Grand River connects it to the lake and a fish ladder has made Grand Rapids a popular location for lake trout and spawning salmon. Muskegon is located directly on Lake Michigan.

[3]Data from the infant medical records were used to assign infants at-risk scores based on questions from the Postnatal Complications Scale (PCS)(Littman and Parmelee, 1978). The PCS is based on 10 items considered to reflect increased risk of mortality and morbidity to newborns, such as respiratory distress, infection, hyperbilirubinemia, and metabolic and temperature disturbances. The PCS uses an optimal scoring technique, such that high scores indicate few complications.

[4]If the father was a student, his father's education and occupation were used to estimate the family's socioeconomic status. In those cases in which the mother was unmarried, socioeconomic status was based on the occupation and education of the individual from whom the family was receiving most of its financial support.

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The sample was also homogeneous in terms of maternal education and age. Only 7.7 percent of the mothers failed to complete high school, while 18.2 percent completed college. Eighty-one percent were between 18 and 30 yr of age and only 3.2 percent over 35. Fifty-seven percent attended prenatal birth classes; 95.8 percent began prenatal medical care by the fourth month of pregnancy, and the remaining 13 women by the sixth month. Their scores on the Obstetrical Complications Scale (OCS)(Littman and Parmelee, 1978)[5] ranged from a minimum of 63 percent to a maximum of 98 percent optimal, with a median of 85 percent optimal, suggesting little variability in obstetrical history.

The sample was selected to over-represent women who had consumed Lake Michigan fish during some time in their lives. The majority (77%) reported consuming moderate to large quantities of Lake Michigan fish, while the rest (23%) reported consuming none of these fish. This design permits two types of analyses. First, adverse effects can be identified by comparing women who consume Lake Michigan fish with those who do not. Additional analyses can be performed to determine the statistical magnitude of the toxic effects and the particular dose-response relationships.

Procedure

Preliminary Screening

To ensure participation of infants likely to have been exposed *in utero* to a broad range of PCB levels, women were screened for past and present consumption of Lake Michigan fish on the morning following delivery. A questionnaire was used to ascertain the source,[6] amount, and kind of fish consumed in the year prior to the infant's birth, and the number of years of fish consumption at that rate. Women were also asked if there was a time in the past (dating back to 1966) when they ate greater amounts of Lake Michigan fish (e.g., the woman grew up in a family in which the father was a sports fisherman). If so, the amount and kind of fish consumed in the past, as well as the number of years of consumption at that rate, were recorded.

---

[5]Data from the maternal interview and medical records are used to assign mothers at-risk scores based on 41 questions in the OCS (Littman and Parmelee, 1978). The OCS score is derived from data relating to pregnancy, such as maternal infection, bleeding, parity, age; the reproductive history, such as previous premature births or stillbirths; and the delivery, such as obstetric medication, duration of labor, type of delivery, and birth weight. Like the PCS, the OCS is based on optimal scoring with high scores reflecting few complications.

[6]Lake Michigan was the primary source of fish. In addition, coho and chinook salmon and lake trout from rivers and lakes connected to Lake Michigan were included since these fish are normal inhabitants of the lake populations.

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TABLE 2

Characteristics of the Sample at Birth (N = 313)

Assessment Parameter	Mean (SD)	Range
Infant characteristics		
Birth weight (g)	3502.7 (560.3)	909.1 -5028.9
Crown-heel length (cm)	51.1 (2.5)	28.5 - 56.0
Head circumference (cm)	35.1 (1.4)	30.5 - 41.3
Ponderal index[a]	2.7 (0.3)	1.9 - 5.6
Gestational age (weeks)[b]	39.9 (2.3)	26.9 - 45.9
Apgar scores		
1-minute	7.9 (1.3)	1.0 - 9.0
5-minute	8.9 (0.8)	2.0 - 10.0
Postnatal complications score[c]	0.9 (0.1)	0.2 - 1.0
Family characteristics		
Socioeconomic status (SES)[d]	39.3 (13.5)	14.0 - 66.0
Maternal age	26.1 (4.6)	18.0 - 42.0
Maternal education (years)	13.3 (1.9)	10.0 - 19.0
Marital status (married)[e]	283.0 (90.4)	--
Obstetrical complications score[f]	84.0 (0.1)	0.6 - 1.0

[a]Based on equation (Miller and Hassanein, 1971):
$$\frac{\text{birth weight (g)} \times 100}{\text{crown-heel length (cm)}^3}$$
[b]Based on obstetrician's estimated date of confinement
[c]Based on PCS (Littman and Parmelee, 1978)
[d]Based on Hollingshead index (n.d.)
[e]N is presented rather than mean; percent of women married in parentheses
[f]Based on OCS (Littman and Parmelee, 1978)

Sampling for contaminants in Lake Michigan fish has shown that most species tested contain detectable levels of PCBs, with especially high levels in fatty species, such as salmon and lake trout (IJC, 1978; Swain, 1981; Willford et al., 1976). These fish, although high in PCB contamination, may be eaten in small quantities, while other less contaminated fish, such as perch or smelt, may be eaten in large quantities. To obtain a more accurate measure of contaminated fish consumption, a weighted value was assigned to each fish species based on average contaminant levels for the species (Table 3). The range of values was normalized to lake trout, salmon, carp, and catfish, species containing the highest concentrations of PCBs (e.g., a fish having half the average PCB level of salmon or lake trout would be weighted 0.5).

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The following equation was used to estimate the mother's annual rate of consumption for each type of fish:

Relative PCB Fish Weight		Number of Fish Meals/Year		0.23 kg (1 Fish Meal)	=	PCB-kg Per Year
	X		X			

This measure is summed across species for each individual to determine a woman's annual fish consumption rate. To estimate cumulative exposure, annual PCB fish consumption rate was multiplied by the number of years the mother reported eating contaminated fish at that rate. If she reported eating contaminated fish at a higher rate in the past, the number of years at the current and past rates were determined separately and then multiplied by their respective consumption rates to yield a measure of cumulative exposure as follows:

Present PCB kg/ Year		Number of Years at Present Rate	+	Past PCB kg/ Year	X	Number of Years at Past Rate	=	Cumulative Consumption (PCB-kg)
	X							

TABLE 3

Relative PCB Values of Lake Michigan Fish[a]

Type of Fish	PCB Weighted Value
Chinook salmon	1.0
Coho salmon	1.0
Lake trout	1.0
Carp	1.0
Catfish	1.0
Bullhead	0.6
Pike or pickerel	0.6
German brown trout	0.4
Perch	0.4
Walleye	0.4
White sucker	0.4
Alewife	0.3
Burbot	0.2
Steelhead or rainbow trout	0.2
Brook trout	0.2
Menominee (round whitefish)	0.1
Smelts	0.1
Whitefish and chubbs (herring)	0.1

[a]Derived from data supplied by the Large Lakes Research Station, U.S. Environmental Protection Agency, Grosse Ile, Michigan

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Sampling Criteria: Exposed and Unexposed

Two criteria were used to determine inclusion of women in the study:

(1) If cumulative exposure within a 6 yr period reported by the mother was equal to 11.8 kg (26 pounds) or more of contaminated fish, the mother qualified for inclusion in the study. This criterion was based on evidence that PCBs are retained in body tissues over relatively long periods of time (Humphrey, 1976).

(2) In addition, a control group was selected comprised of newly-delivered mothers who reported consuming no Lake Michigan fish in the past or during pregnancy.

Of the 8,482 women screened (i.e., 96% of all maternity patients in the four participating hospitals), about 4 percent or 343 ate PCB-contaminated fish in sufficient quantities to qualify for inclusion in the exposed group.[7] About 29.3 percent of the women screened reported eating no Lake Michigan fish; 4.6 percent or 114 of these women were invited to serve as controls. As a check on whether women invited to participate in the study, either as fish eaters or as controls, were similar demographically to women who were not asked to participate, a demographic comparison group was selected by matching each potential participant with the next woman whose screening interview followed her own. This procedure assured a comparison group matched for hospital and approximate date of delivery with the potential sample of exposed and nonexposed mothers. Women invited to participate did not differ significantly from others in their community in socioeconomic status, maternal age, education, marital status, or sex of infant (Table 4). Among those women invited to participate, fish eaters did not differ from control women on these variables (Table 5).

Of the 457 women invited to participate, 144 (32%) refused. Mothers who consented to participate were more educated than refusers, suggesting that greater education may be associated with greater interest in research. Among women who agreed to participate, exposed and non-exposed control groups did not differ in socioeconomic status, maternal age or education, number of offspring (parity), or sex of infant (Table 6). While slightly more of the exposed women were married, this difference was not statistically significant ($p > 0.05$).

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[7]The qualification rate of 4 percent of the population screened, coupled with demographic data on the 18 county areas adjacent to Lake Michigan, suggests that almost 100,000 women in this region might qualify as high fish eaters. These figures do not include women in nearby Wisconsin, considered the salmon capital of the world, or those from the Chicago area.

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TABLE 4

Characteristics of Qualifier and Demographic Comparison Groups (N=914)

Assessment Parameter	Qualifiers: Exposed and Control Groups (N=457) Mean	(SD)	Demographic Comparison Group (N=457) Mean	(SD)	t
Socioeconomic status (SES)[a]	38.5	(13.1)	37.6	(12.9)	1.10
Maternal age	25.9	(4.5)	25.9	(4.8)	0.05
Maternal education (yr)	13.2	(1.9)	12.9	(2.0)	1.88
	N	(%)	N	(%)	χ^2
Marital status (married)	419	(91.7)	413	(90.4)	0.18
Sex of infant (male)	224	(49.6)	241	(53.9)	1.71

[a]Based on Hollingshead index (n.d.)

Note: Data on SES, maternal age, and sex of infant were unavailable as follows: SES was unavailable for eight qualifiers and ten comparison women; sex of infant for five qualifiers and ten comparison women; maternal age for one comparison woman.

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TABLE 5

Comparison of Qualifying Exposed and Control Groups (N=457)

Assessment Parameter	Qualifying Exposed Group (N=345) Mean	(SD)	Qualifying Control Group (N=112) Mean	(SD)	t
Socioeconomic status (SES)[a]	38.3	(13.1)	39.4	(13.2)	-0.76
Maternal age	26.0	(4.6)	25.4	(4.3)	1.33
Maternal education (yr)	13.1	(1.9)	13.2	(1.9)	-0.44
	N	(%)	N	(%)	χ^2
Marital status (married)	319	(92.5)	100	(89.3)	1.12
Sex of infant (male)	167	(49.4)	54	(49.5)	0.00

[a]Based on Hollingshead index (n.d.)

Note: Data were unavailable on SES for six exposed and two control women; sex for seven exposed and three control infants.

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TABLE 6

Study Sample: Exposure and Control Groups (N=313)

Assessment Parameter	Exposure Group (N=242) Mean	(SD)	Control Group (N=71) Mean	(SD)	t
Socioeconomic status (SES)[a]	39.3	(13.6)	39.5	(13.4)	-0.14
Maternal age	26.2	(4.7)	25.7	(4.5)	0.81
Maternal education (yr)	13.3	(1.9)	13.3	(2.0)	0.15
	N	(%)	N	(%)	χ^2
Marital status (married)	223	(92.1)	60	(84.5)	3.70
Sex of infant (male)	124	(51.2)	40	(56.3)	0.39
Parity (first-borns)	100	(42.2)	32	(45.1)	0.18

[a]SES, based on Hollingshead index (n.d.), was unavailable for three exposed women

Measures of Exposure

PCB-Fish Consumption. The principal measures of contaminated fish consumption were:

(1) highest annual rate of PCB-fish consumption;
(2) cumulative PCB-fish consumption; and
(3) rate of PCB-fish consumption during pregnancy.

These measures were weighted for the contaminant levels of the species reported by the mothers. The first measure (highest annual rate) reflects findings from previous studies that the highest level of contaminated fish consumption predicts subsequent PCB serum levels (Humphrey, 1976), findings consistent with the tendency of PCBs to be poorly metabolized. But PCBs tend to accumulate in body tissues over time, and prediction might be improved when reported values and years at these levels are taken into account. The measure of cumulative PCB-fish consumption, which sums rates over years after normalizing each component of the measure to z scores, was constructed to assess this possibility. The third measure, rate of PCB-fish consumption during pregnancy, was used to

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assess a somewhat different possibility (i.e., that the impact on the infant is especially pronounced when the mother consumes contaminated fish during pregnancy). PCB-kg refers to a fish consumption score weighted by the contaminant levels of the species reported by the mother. Mean annual rate of PCB-fish consumption at the highest levels reported by the exposed mothers was 6.7 PCB-kg (14.7 PCB-pounds) per yr (SD = 5.8 PCB-kg, range = 1.2 to 41.7 kg/yr). This rate is equivalent to about 0.6 PCB-kg per month or 2 to 3 salmon or lake trout meals (at 0.2 kg/meal). The women reported eating Lake Michigan fish for an average of 16.1 yr (SD = 9.0, range = 1.0 to 40.0 yr). In the year preceding the infant's birth, mean level of fish consumption was 4.4 PCB-kg (9.7 PCB-pounds; SD = 4.4 PCB-kg, range = 0.0 to 26.5 PCB-kg). Therefore, the selection procedure described earlier yielded a range of exposure levels with specific values depending on the particular measure of maternal fish consumption used. The fish consumption variables were positively skewed and were normalized by means of log transformations. One outlier, a women who reported ingesting 54.5 kg of contaminated fish in one year, was eliminated from the analyses.

Laboratory Analyses

Hospital personnel collected samples of umbilical cord blood for every infant born in the participating hospitals at the time of delivery. Cord blood specimens for newborns in the sample were available, therefore, for laboratory analysis, while those of non-participants were discarded shortly thereafter. Samples of maternal blood were collected on the second day following delivery as part of routine blood tests. Sixty-one percent of the infants in the sample were breast fed; and of those, 70.3 percent of the mothers provided breast milk samples between 1 and 16 weeks after delivery. A second sample of breast milk was collected from 45 women who continued breast feeding at 5 months.

Analyses of cord serum, maternal serum, and breast milk samples for PCBs were performed at the Michigan Department of Public Health by means of packed column gas chromatography (Burse et al., 1980; Needham et al., 1981). A 4 ml sample of serum was mixed with 2 ml methanol. This mixture was extracted with 5 ml hexane/diethyl ether (1:1, v/v) three times by agitating on a rotary mixer 15 to 20 minutes at 50 to 55 rpm. The extracts were combined in a Kontes concentrator tube, reduced to a small volume (about 0.5 ml), and transferred quantitatively to a miniature Florisil cleanup column from which PBBs, PCBs, and chlorinated hydrocarbon pesticides were eluted with 6 percent diethyl ether/petroleum ether mixture (v/v). The eluate was concentrated to a small volume (1.0 ml), transferred with three x 1.0 ml rinsings of hexane to a column of Silica Gel 60, and eluted with hexane to separate PCBs from the chlorinated hydrocarbon pesticide group (Picer and Ahel, 1978). The fraction containing PCBs, PBBs, and DDE was concentrated to 2 ml and analyzed by electron-capture gas chromatography with a 3 percent SE-30 column. Injector, initial column, final column, and detector temperatures were 240°C, 160°C, 210°C, and

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320°C, respectively. Quantification was provided by adapting the Webb-McCall method (Sawyer, 1978; Webb and McCall, 1973) to a computer data system with Aroclors 1016 and 1260 used as calibration standards. Estimation of PCB levels in sample extracts was based on comparison of peaks on the chromatogram with respective peaks of known concentrations in the reference standards. The Aroclor 1016 portion of the chromatogram was used to estimate the quantity of lower chlorinated congeners, while the 1260 portion was applied to measure levels of more highly chlorinated congeners and isomers. Limits of detection were 5 ng/ml for Aroclor 1016 and 3 ng/ml for Aroclor 1260 in the sample extracts. Quality control over time was ensured by addition of a spiked sample of bovine serum with every batch of 10 samples, as well as the use of a glassware blank and a reagent blank. Serum lipids were determined colorimetrically using the Dade Total Standard for plotting the calibration curve of concentration vs. absorbence (Fringe et al., 1972).

A similar procedure was used in analyzing breast milk samples. A 5 g sample of breast milk in a screw-capped (teflon-lined) culture tube was mixed with 0.1 g of potassium oxalate and 5 ml methanol. This mixture was extracted in the same manner as serum samples. Extracts were combined in a micro distilling assembly and concentrated to a small volume. Evaporation of solvent from the concentrated extract was conducted in a small preweighed aluminum dish and the residue dried under vacuum in a desiccator. In contrast to serum analysis, wherein lipid levels were estimated, lipid content of the breast milk sample was determined gravimetrically. The lipid residue was then redissolved in a small amount of petroleum ether and transferred quantitatively to a miniature Florisil cleanup column. Subsequent procedures for serum were then applied to the breast milk analyses.[8] (For a review of technical problems associated with these analytical procedures, see IARC Monograph, 1978; Mullin et al., 1983; Humphrey, 1976.)

All serum samples containing lipid levels below 200 mg/dl were omitted from the data analyses, since measurement techniques were judged to be insufficiently sensitive to detect PCB levels at lipid values of this magnitude. The removal of three maternal serum and 43 cord serum samples for this reason did not alter the fundamental nature of the PCB distribution. Twenty-seven additional cord blood samples could not be analyzed because insufficient quantities had been collected, the hospital had mistakenly discarded them, or because of equipment failures in the laboratory. Included in the following analyses were 198 cord serum and 196 maternal serum samples, and 138 neonatal and 45 five-month breast milk samples.

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[8]The summary of the laboratory techniques used to analyze the serum and breast milk samples was written in conjunction with Dr. Harold A. Price of the Michigan Department of Public Health.

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RESULTS

Laboratory results for cord serum, maternal serum, and breast milk samples are presented in Table 7. The column labeled "nondetectable" refers to PCB values of 0.1 ng/ml to five times the noise level on the chromatogram; the right hand column refers to PCB levels that are detectable, but still below the laboratory's quantification limits. The majority of the PCB levels matched to the 1016 standard were below quantification limits. This was particularly true for the cord and maternal sera analyses. Among these samples, only one of 195 and five of 190 cases, respectively, were quantifiable. Since comparisons with the 1260 standard yielded considerably fewer values below the quantification limit, 1260 values may provide a more reliable measure of PCB body burden. Arithmetic means for the more highly chlorinated isomers exceeded the lower chlorinated isomers by a ratio of 2.7 to 1 for the cord samples and as much as 5.5 to 1 for the neonatal breast milk samples. This differential presumably results from the tendency of lower chlorinated isomers to be less stable, more susceptible to degradation in the environment, and metabolized more rapidly in the organism (Matthews, 1983).

PCB levels for a large proportion of the cord serum samples were not quantifiable, even when the 1260 standard was used. A pair-wise comparison of PCB 1260 serum levels on a whole basis indicates that mean PCB levels in maternal serum were substantially higher than in cord serum (Table 8), confirming previous findings (Akiyama et al., 1975; Kodama and Ota, 1977). Masuda et al. (1978) found a similar differential in a recent Japanese sample and concluded that the placenta may act as a partial barrier to PCBs. However, in the present sample lipid levels in maternal serum are twice those in cord serum. When PCB concentrations are calculated on a fat basis, the mean PCB values are similar for the cord and maternal sera (Table 8), and the differential is no longer significant. Thus, four studies provide evidence that PCBs cross the placenta, thereby exposing the fetus.

PCB values were also obtained for two samples of breast milk, one during the first few weeks after birth and a more limited sample when the infant was 5 months old. Matched pair t-tests indicate that PCB levels on a whole basis were substantially higher in breast milk than cord and maternal sera samples. Again, when samples were compared on a fat basis, differences were no longer significant. Kodama and Ota (1980) suggested that breast feeding may decrease PCB body burden in the mother. Although PCB concentrations in the breast milk of nursing mothers in our sample tended to decline over time, this decline was not significant.

Correlations among PCB levels in the four biological specimens are shown in Table 9. The highly significant correlation of cord with maternal serum levels provides further evidence for the transplacental passage of the PCB molecule and corroborates a similar relation reported by Masuda et al. (1978) and Kodama and Ota (1977), using smaller samples of women. The significant correlation between PCBs in maternal serum and

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TABLE 7

Polychlorinated Biphenyls in Cord Serum, Maternal Serum, and Maternal Breast Milk (Whole Basis)

Assessment Parameters	N	Mean (SD)	Median	Nondetectable[a] N (%)	Detectable But Nonquantifiable[b] N (%)
Cord serum (ng/ml)					
1016 standard	195	0.9 (0.9)	0.6	23 (11.8)	171 (87.7)
1260 standard	198	2.5 (1.9)	2.0	4 (2.0)	130 (65.7)
Maternal serum (ng/ml)					
1016 standard	190	1.6 (4.5)	0.8	16 (8.4)	169 (88.9)
1260 standard	196	5.5 (3.7)	4.6	0 (0.0)	44 (22.4)
Breast milk - neonatal (ng/g)					
1016 standard	138	4.1 (4.5)	2.9	11 (8.0)	85 (61.6)
1260 standard	138	22.5 (12.3)	20.4	0 (0.0)	2 (1.4)
Breast milk - 5 months (ng/g)					
1016 standard	45	3.7 (3.4)	2.8	3 (6.7)	30 (66.7)
1260 standard	45	17.4 (12.1)	14.1	0 (0.0)	4 (8.9)

[a]Nondetectable refers to values of 0.1 ng/ml to five times the noise level of the chromatogram
[b]Nonquantifiable refers to detectable levels below the quantifiable limits of 5 ng/ml for Aroclor 1016 and 3 ng/ml for Aroclor 1260

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TABLE 8

Pairwise Comparisons of PCBs and Lipids in Cord Serum, Maternal Serum, and Maternal Breast Milk (1260 Standard)

Assessment Parameters	N	Whole Basis (ng/ml or ng/g)[a] Mean (SD)	t	Fat Basis (ng/g) Mean (SD)	t	Lipids Percent	t
Cord serum	148	2.4 (1.9)	-10.18[b]	788.1 (696.5)	-0.82	0.32	-25.69[b]
Maternal serum		5.3 (3.7)		835.3 (557.1)		0.64	
Cord serum	95	2.4 (1.8)	-15.45[b]	824.2 (714.2)	0.13	0.31	-20.45[b]
Breast milk - neonatal		22.8 (13.0)		813.9 (377.9)		2.89	
Maternal serum	91	5.6 (3.2)	-13.36[b]	932.2 (579.1)	1.55	0.63	-17.06[b]
Breast milk - neonatal		22.7 (12.3)		827.8 (380.4)		2.85	
Breast milk - neonatal	42	20.0 (9.3)	1.31	750.5 (408.8)	-0.19	2.96	0.51
Breast milk - 5 month		18.0 (12.2)		772.3 (671.2)		2.82	

[a]Cord and maternal sera values on a whole basis are given in ng/ml and breast milk values in ng/g

[b]$p < 0.0001$

TABLE 9

Intercorrelations of Log PCBs (1260 Standard) in Cord Serum, Maternal Serum, and Maternal Breast Milk

Assessment Parameter	Cord Serum	Maternal Serum	Breast Milk Neonatal	Breast Milk 5 Month
Cord serum	--	0.41[a] (148)	0.09 (95)	-0.06 (25)
Maternal serum	0.43[a] (145)	--	0.23[b] (91)	0.01 (30)
Breast milk - neonatal	0.16 (93)	0.28[c] (91)	--	0.61[a] (42)
Breast milk - 5 month	-0.01 (24)	-0.10 (30)	.30[b] (42)	--

[a] $p < 0.0001$
[b] $p < 0.05$
[c] $p < 0.01$

Note: Rs above the main diagonal are values calculated on a whole basis, while those below are on a fat basis. N appears in parentheses. Lipid values were missing for three cord serum samples, two neonatal breast milk samples, and one 5-month breast milk sample.

breast milk indicates that PCBs are moderately stable in the mother, an inference further supported by the significant correlations between breast milk samples obtained shortly after the baby's birth and those obtained at 5 months.

Correlations between maternal and cord sera were similar in magnitude, whether calculated on a whole serum or fat basis, $r = 0.41$ and 0.43, respectively (Table 9). While the whole and fat basis findings were also similar for correlations between maternal serum and breast milk, the two approaches yielded different results for the neonatal to 5-month breast milk correlation.

Consistency between analyses derived on a whole and fat basis was also indicated by the pattern of the intercorrelations shown in Table 10. PCB levels in the cord and maternal sera on a whole serum basis were highly correlated with levels calculated on a fat basis ($r = 0.93$). Thus, for serum, it seems to make little difference whether measures are derived on a whole or fat basis. Although cord and maternal sera are low in lipids, lipid levels tend to be relatively stable. Because breast milk lipids fluctuate considerably, the same consistency does not appear for breast milk values derived by the two

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TABLE 10

Intercorrelations of Log PCBs (1260 Standard) in Cord Serum, Maternal Serum, and Maternal Breast Milk

	Whole Basis			
Assessment Parameter	Cord Serum	Maternal Serum	Breast Milk Neonatal	Breast Milk 5 Month
Fat basis				
Cord serum	0.93[a] (194)	0.37[a] (145)	0.07 (93)	0.05 (24)
Maternal serum	0.43[a] (148)	0.93[a] (196)	0.20[b] (91)	0.01 (30)
Breast milk - neonatal	0.16 (95)	0.35[a] (91)	0.62[a] (138)	0.30[c] (42)
Breast milk - 5 month	-0.06 (25)	-0.08 (30)	0.08 (42)	0.39[d] (45)

[a] $p < 0.001$
[b] $p < 0.10$
[c] $p < 0.05$
[d] $p < 0.01$

Note: N appears in parentheses.

methods. This apparent instability suggests that in the analyses of breast milk, measures that take lipid fluctuation into account are likely to be more reliable.

These findings were further supported by an analysis of the degree to which PCB levels could be predicted from lipid levels in serum or breast milk. While the PCB levels in the cord and maternal sera were unrelated to corresponding cord and maternal lipid levels, there was a significant association between PCB and lipid levels in the neonatal and 5 month breast milk ($r = 0.58$, $p < 0.0001$; and $r = 0.63$, $p < 0.0001$, respectively).

Women and their offspring were selected for the study on the basis of reported fish consumption patterns. Levels of fish consumption reported by the exposed and control mothers for whom the different biological measures were available are shown in Table 11. When women who breast fed were compared with those who did not, no difference was found for highest annual rate or cumulative consumption measures. While their rate during pregnancy was slightly lower than the rest of the sample ($M = 2.9$ vs. 3.8 PCB-kg/yr), the difference failed to

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TABLE 11

Levels of Reported Contaminated Fish Consumption (PCB-kg) of Women Providing Blood and Breast Milk Samples

Assessment Parameters	N	Mean (SD)	Median	Range
Cord serum analyses				
Consumption at highest rate	198	4.3 (5.5)	3.0	ND - 41.7
Consumption during pregnancy	189	2.8 (3.9)	1.9	ND - 22.4
Cumulative consumption	198	61.3 (97.8)	27.8	ND - 716.6
Maternal serum analyses				
Consumption at highest rate	196	4.4 (5.5)	3.2	ND - 41.7
Consumption during pregnancy	190	2.8 (3.6)	2.2	ND - 22.4
Cumulative consumption	196	62.4 (97.5)	28.6	ND - 716.6
Breast milk - neonatal				
Consumption at highest rate	138	4.7 (5.3)	3.3	ND - 41.7
Consumption during pregnancy	135	2.9 (3.5)	2.2	ND - 20.0
Cumulative consumption	138	62.9 (90.9)	38.4	ND - 716.6
Breast milk - 5 month				
Consumption at highest rate	45	5.5 (8.0)	3.8	ND - 41.7
Consumption during pregnancy	45	2.8 (2.9)	2.2	ND - 9.5
Cumulative consumption	45	82.5 (135.3)	43.4	ND - 716.6

Note: Consumption levels include data on exposed and control women.

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reach conventional levels of statistical significance (t = 1.90, $p < 0.10$).

Correlations between maternal reports of contaminated fish consumption and the four biological measures of PCB body burden are presented in Table 12. No relationship was found between cord serum PCB levels and maternal fish consumption, possibly because of the detection problems in cord serum analysis described earlier. In contrast, a positive correlation was found between PCB levels in maternal serum and all three reported fish consumption measures. Mean PCB level in maternal serum was 6.1 ng/ml (SD = 3.7) among women who ate contaminated fish, as contrasted to 4.1 ng/ml (SD = 2.7) among those who abstained (t = 3.83, $p < 0.0001$). These data replicate in a sample of women of child-bearing age Humphrey's (1976) finding that Lake Michigan fish consumption predicts PCB body burden in Michigan residents. The data extend this finding by showing a significant correlation between fish consumption and PCB levels in neonatal breast milk. Mean PCB residues were higher in breast milk samples of exposed than in samples of nonexposed women (M = 865.6 vs. 622.2 ng/g on a fat basis, t = 3.21, $p < 0.005$). The lack of a consistent relationship between maternal report of prenatal fish consumption and breast milk levels at 5 months may be due in part to postpartum ingestion of contaminated fish, which will be examined in future analyses. Figure 2 shows a scatterplot demonstrating the linear relationships between maternal serum 1260 and fish consumption at the highest annual rate. For every pound of contaminated fish ingested by the mother, the PCBs in her serum increase by about 0.15 ng/ml on a whole basis or 23.6 ng/g on a fat basis.

DISCUSSION

Despite their widespread distribution in our environment and concern about human accumulation, few studies are currently available on the serum PCB levels of individuals chronically exposed to PCBs via their diet. Moreover, the toxicology of PCBs is little understood in comparison with that of other xenobiotic chemicals, such as DDT and BHC (Hirayama, 1976; Yoshimura and Yoshimura, 1976). The present longitudinal study was designed to investigate effects of PCB exposure from contaminated fish consumption on two potential at-risk groups, pregnant women and their newborn offspring. While several reports have appeared on the transfer of PCBs from mother to child via breast milk (e.g., Kodama and Ota, 1980; Kuwabara *et al.*, 1979), only a few studies examined the transfer of PCBs *in utero* (Akiyama *et al.*, 1975; Kodama and Ota, 1980; Masuda *et al.*, 1978). These studies used either relatively small unexposed samples or women and infants exposed during the Yusho incident. No study to date has examined the pattern of transfer from mothers to offspring exposed via the food chain.

The data in this report provide empirical support for linkages between source of contamination and body burden shown in the analytic model (Figure 1). They also provide evidence of the preponderance of more heavily chlorinated isomers in the serum and breast milk of women whose exposure to PCBs is due

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TABLE 12

Correlations Between Log Contaminated Fish Consumption and Log PCBs in Cord Serum, Maternal Serum, and Breast Milk (1260 Standard)

Assessment Parameters	N	r	Regression Equation
Fish consumption at highest annual rate with			
Cord (whole serum basis)	198	0.09	y = 1.05 + 0.04x
Maternal (whole serum basis)	196	0.38[a]	y = 1.47 + 0.15x
Breast milk - neonatal (fat basis)	138	0.30[a]	y = 6.36 + 0.12x
Breast milk - 5 month (fat basis)	45	0.24	y = 6.24 + 0.11x
Fish consumption during pregnancy with			
Cord (whole serum basis)	189	0.13	y = 1.05 + 0.05x
Maternal (whole serum basis)	190	0.31[a]	y = 1.57 + 0.13x
Breast milk - neonatal (fat basis)	135	0.24[b]	y = 6.47 + 0.10x
Breast milk - 5 month (fat basis)	45	0.36[c]	y = 6.19 + 0.18x
Cumulative fish consumption (normalized) with			
Cord (whole serum basis)	198	0.08	y = 1.05 + 0.02x
Maternal (whole serum basis)	196	0.29[a]	y = 1.52 + 0.07x
Breast milk - neonatal (fat basis)	138	0.21[b]	y = 6.38 + 0.06x
Breast milk - 5 month (fat basis)	45	0.10	y = 6.31 + 0.04x

[a] $p < 0.001$
[b] $p < 0.01$
[c] $p < 0.05$

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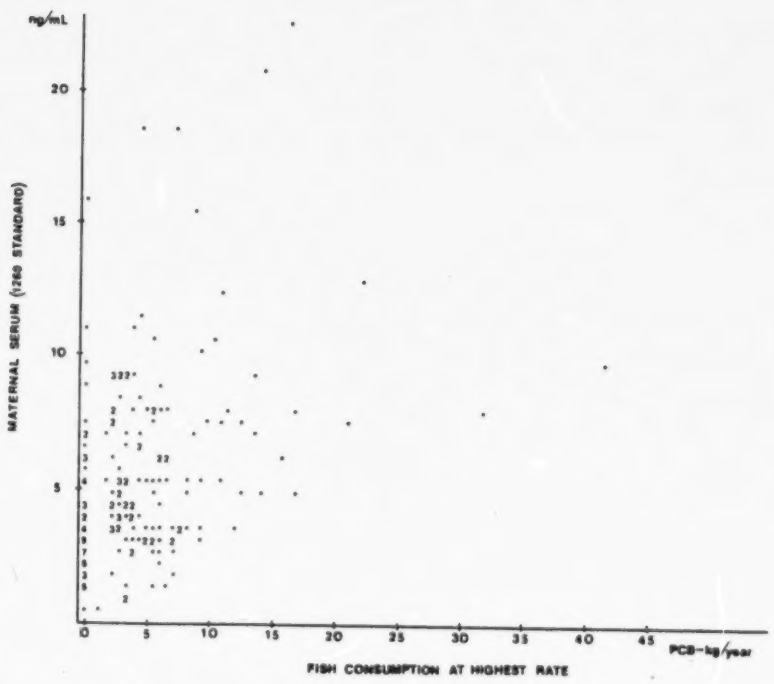

Figure 2. Scatterplot of maternal serum (1260 standard) by fish consumption at the highest annual rate.

in part to the ingestion of contaminated fish. The small amounts of 1016 present in the biological specimens and the poor reliability of their measurement indicate that values matched to the 1260 standard are more likely to yield meaningful findings.

The present study evaluated the linkages from fish consumption to maternal body burden and subsequently to the developing fetus and breast milk. Even though exposure levels were only moderate in the women studied, reported contaminated fish consumption predicted PCB residues in two measures of body burden, maternal serum and breast milk. These results confirm prior studies which found an association between fish consumption and PCB residues in serum specimens (Kreiss et al., 1981; Kuwabara et al., 1979; Humphrey, 1976), while also demonstrating that the relationship holds for younger women, an age group not previously studied. The particular significance of this finding is that PCBs in the environment may pose a risk to the fetus and newborn, since the women in this age group are in the middle of their childbearing years.

Transplacental passage by the PCB molecule was indicated by the significant positive correlation between maternal and

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cord sera (r = 0.41, p < 0.0001), confirming two prior studies which yielded similar findings (r = 0.24, Masuda *et al.*, 1978; r = 0.45, Kodama and Ota, 1977). The transfer of PCBs to breast milk was confirmed by a similar positive correlation (r = 0.27, p < 0.01, for maternal serum on a whole basis to neonatal breast milk on a fat basis), confirming the 1978 finding of Masuda *et al.* (r = 0.29). While cord and maternal sera yield similar results regardless of whether the analysis is performed on a whole serum or fat basis, breast milk residues yield varying results due presumably to fluctuations in lipid levels in breast milk.

The present data are consistent with the notion that PCBs move through the environment and the human body into systems which may potentially threaten the infant both before and after birth (Swain, 1981). At this time it is not clear which of these exposures--prenatal (intrauterine) or postnatal (via breast milk)--has the greater impact on infant development. While the absolute quantity of PCB residues is substantially lower in cord serum than in breast milk, the fetal organism is particularly vulnerable during the prenatal period. One factor that has been overlooked in this debate (e.g., Masuda *et al.*, 1978) is the size of the fetus. When PCB exposure is calculated on the basis of body weight, the infant's prenatal exposure is substantial. In addition, the values for PCBs in cord serum may underestimate actual levels of exposure for reasons discussed earlier. Moreover, different biological systems in the fetus and newborn may be affected depending on the developmental period during which exposure occurs.

The long-term implications for human health of the association between contaminated food ingested at chronic low levels and PCB body burden have only begun to be studied. Unlike findings from studies of persons exposed occupationally to PCBs, preliminary reports suggest possible increases in elevated blood pressure levels (Kreiss *et al.*, 1981) and a greater frequency of reported cancers (Humphrey, 1983) in persons exposed to PCBs through the ingestion of contaminated food. Preliminary analyses of the effect of intrauterine exposure on neonatal behavior indicate a number of subtle behavioral deficits, which may have implications for subsequent development (Fein *et al.*, 1983a). The present study provides empirical support for the use of maternal reports of fish consumption as reliable indicators of PCB exposure, while also predicting transfer of PCBs *in utero* and in the breast milk.

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